United States Environmental Protection Agency

BOSC Site Visit for the National Center for Computational Toxicology

December 17-18-2007

Office of Research and Development
National Center for Computational Toxicology

United States
Environmental Protection
Agency

"…to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals"

www.epa.gov/ncct

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Agenda

- General Overview of Center Activities and Status
- Focal Presentations
  - ToxCast – Dix et al
  - Information Management – Judson et al
  - Virtual Liver – Shah et al
  - Arsenic BBDR – Conolly et al
  - Virtual Embryo – Knudsen et al
- Format for Focal Presentations
  - 45 minute presentation followed by 45 round table discussion

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Your Task to Address these Questions:

1. **Does the scope and involvement….reflect activities consistent with the function of a center?**
2. **Are the goals….suitably described, ambitious and innovative?**
3. **Are there significant gaps in the approach…?**
4. **Does the work offer to significantly improve environmental health impacts and is the path to regulatory acceptance apparent?**
5. **Have appropriate data management and analysis tools been incorporated?**
6. **How would you assess the outreach to other groups?**

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National Exposure Research Laboratory

Human and ecosystem exposure to pollutants

National Center for Environmental Research

Extramural grants in all research areas

National Health and Environmental Effects Research Laboratory

Effects of contaminants on human health and ecosystems

National Risk Management Research Lab

Preventing and reducing risks to humans and the environment

National Center for Computational Toxicology

Merging of computational and molecular approaches

National Homeland Security Research Center

Responses to attacks against buildings and water treatment systems

National Center for Environmental Assessment

Human health and ecological risk assessment

Enabling Technologies

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Molecular Biology

DNA

Transcription

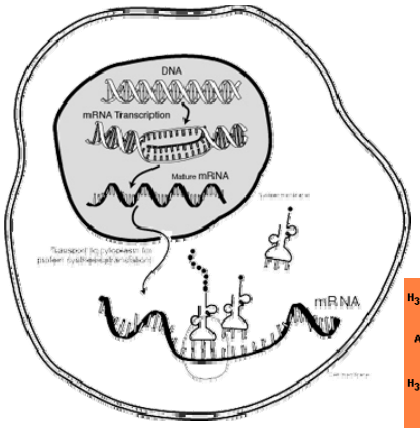
mRNA

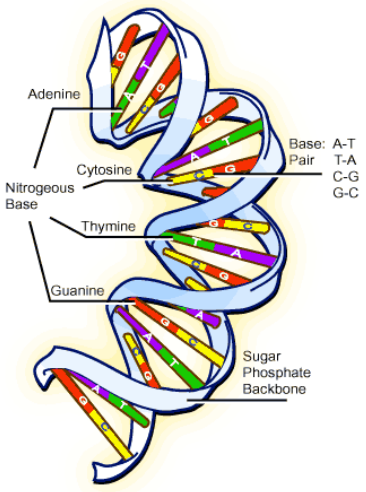
Translation

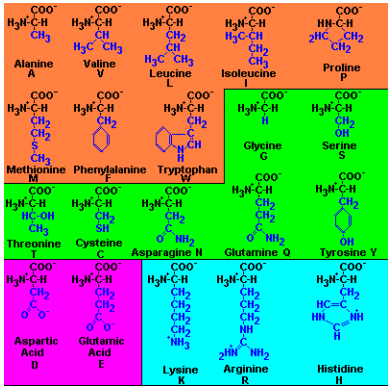
Protein

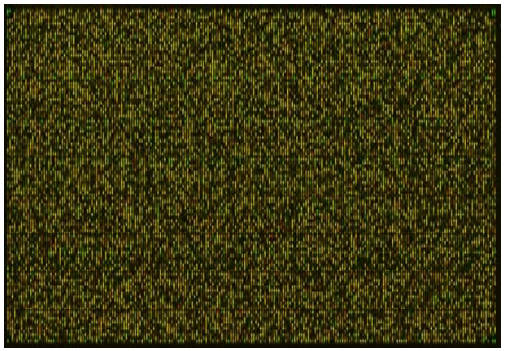
Metabolism

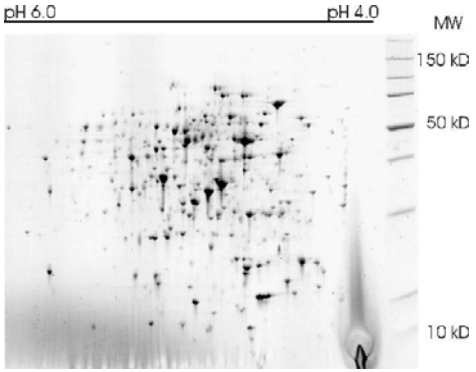
Metabolites

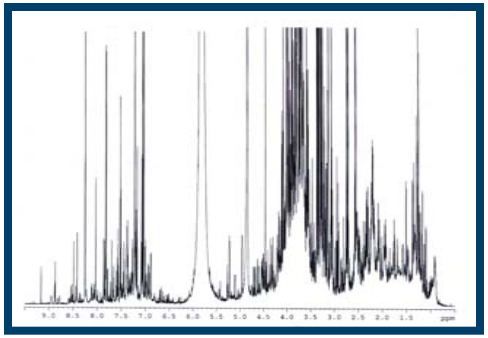












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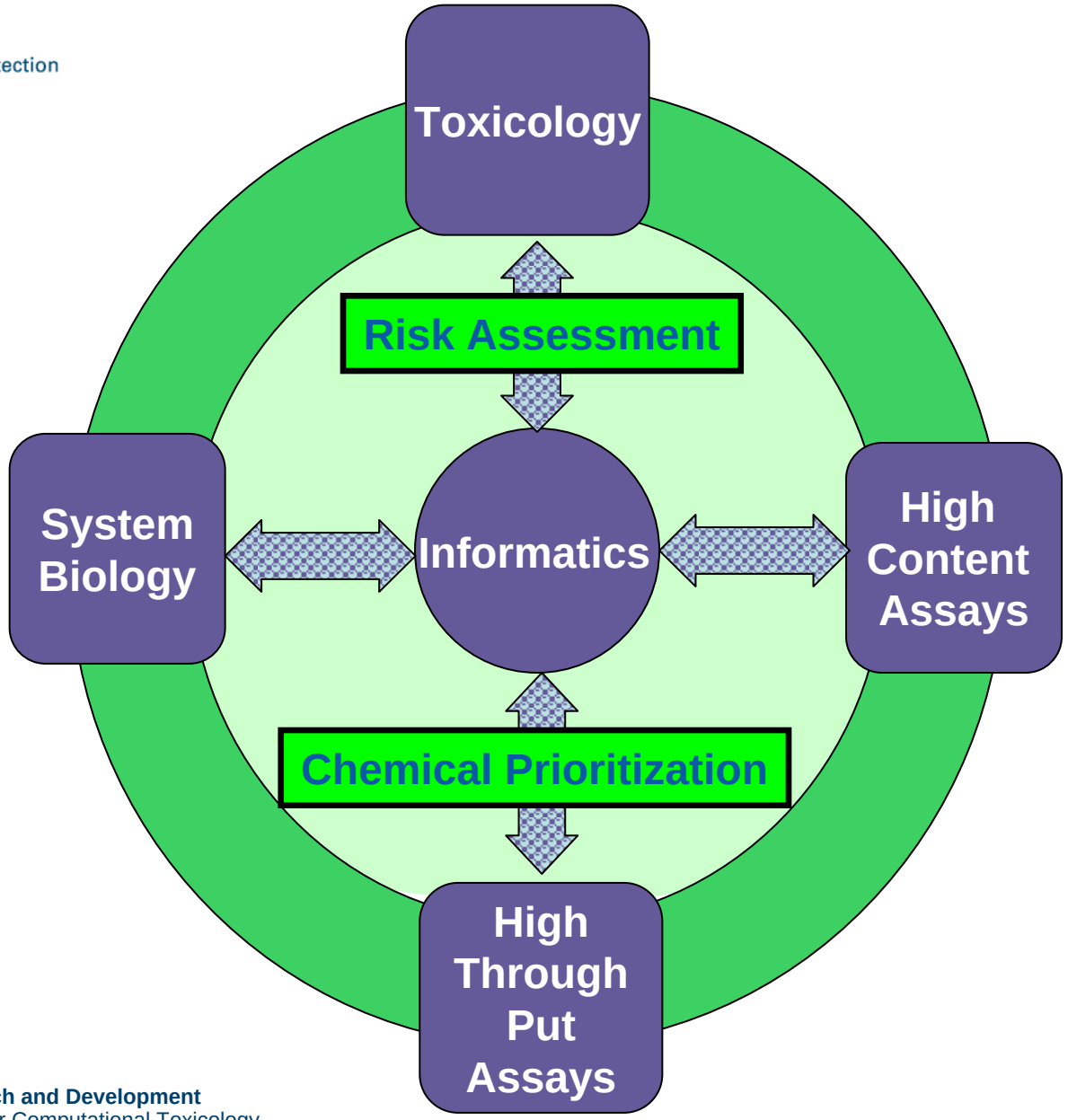
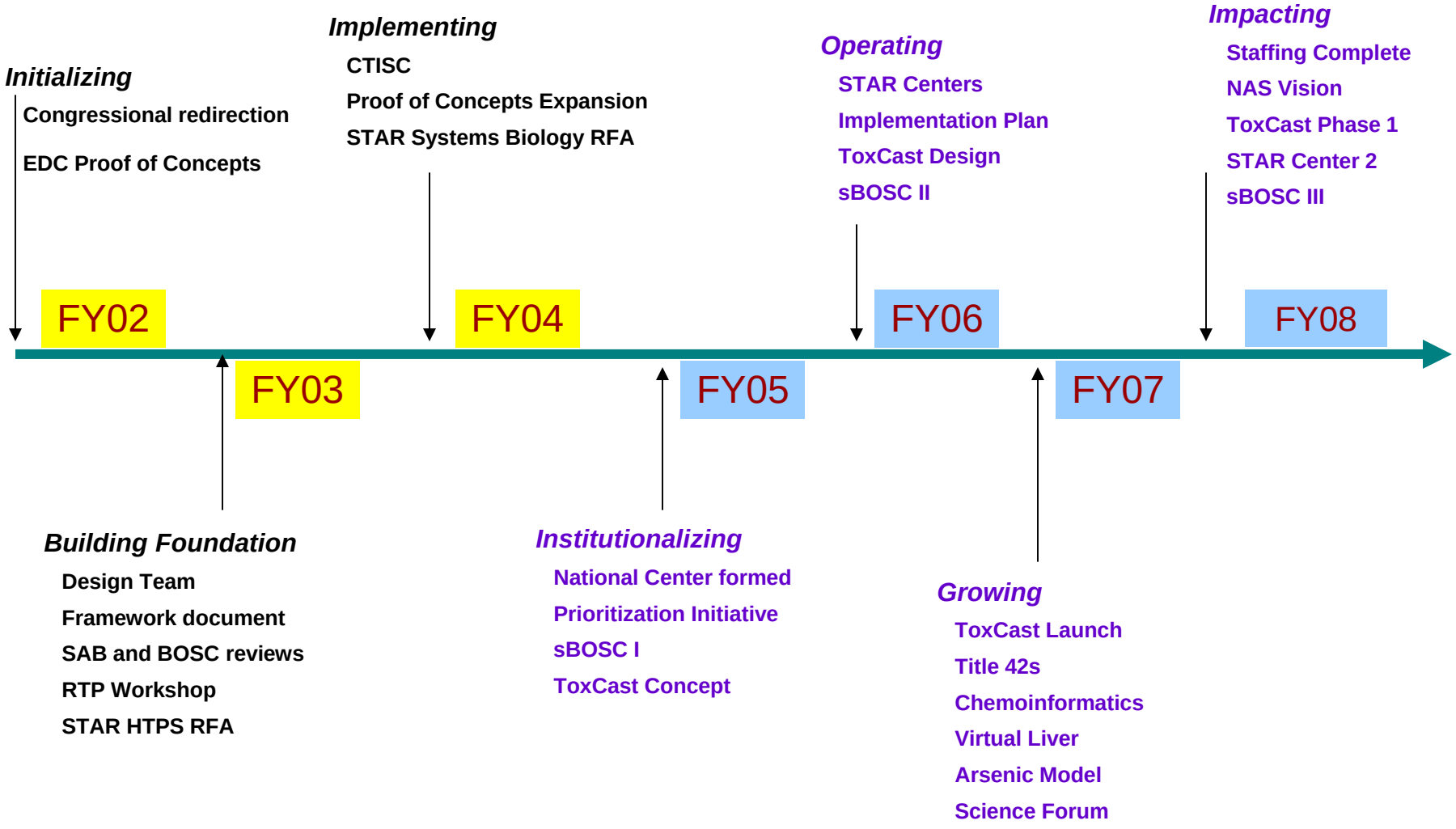
What's It All About

- Digitization
  - Legacy data
  - Dispersed data
- Scale
  - Chemicals
  - Biological space
  - Levels of biological organization
- Quantifying
  - Physiology, biochemical pathways and networks, biology
- Data mining and management


Toxicology
Risk Assessment
System Biology
Informatics
High Content Assays
Chemical Prioritization
High Through Put Assays

Program Development



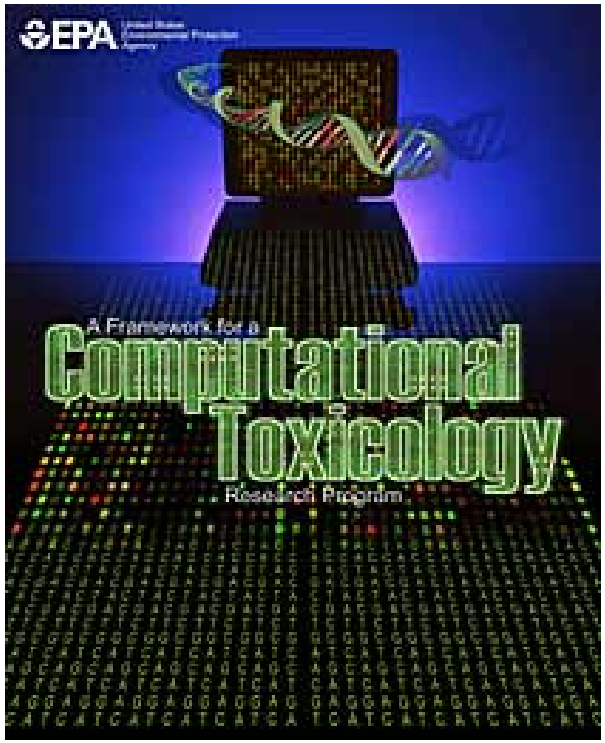
The Framework for a CompTox Program (2003)

Goals:

- **Improve Linkages in the Source to Outcome Paradigm**
- **Provide Predictive Models for Hazard Identification**
- **Improve Quantitative Risk Assessment (Dose, Species, Chemical)**

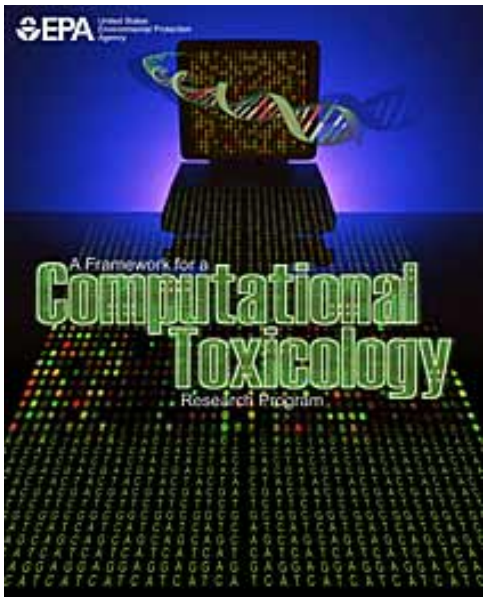
Success:

- **Measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern**



www.epa.gov/comptox

Maturation of the CTRP



2003

ORD's

Computational Toxicology

Research Program

Implementation Plan

(FY 2006 – 2008)

April 2006

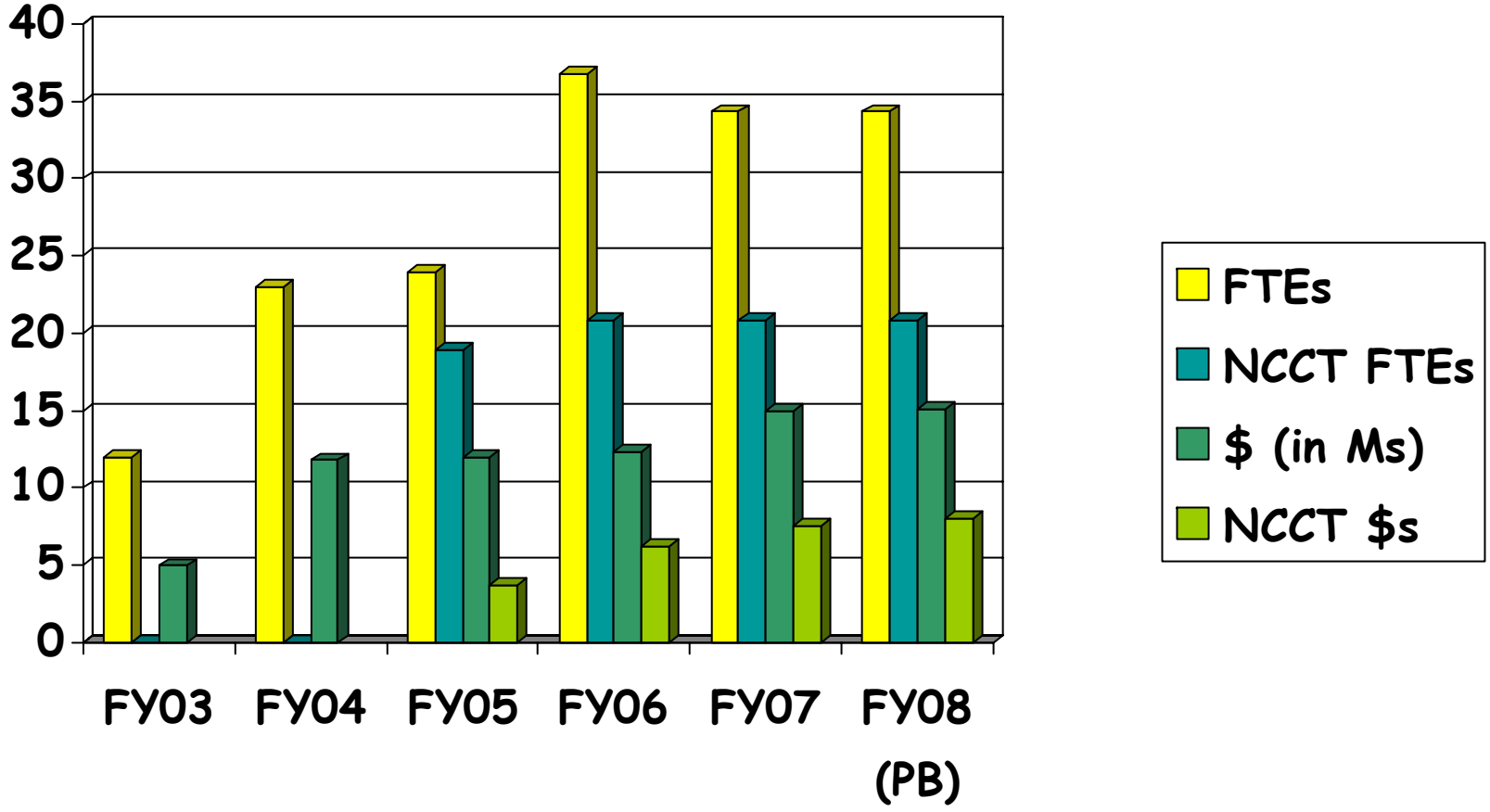
2006

OUTCOMES

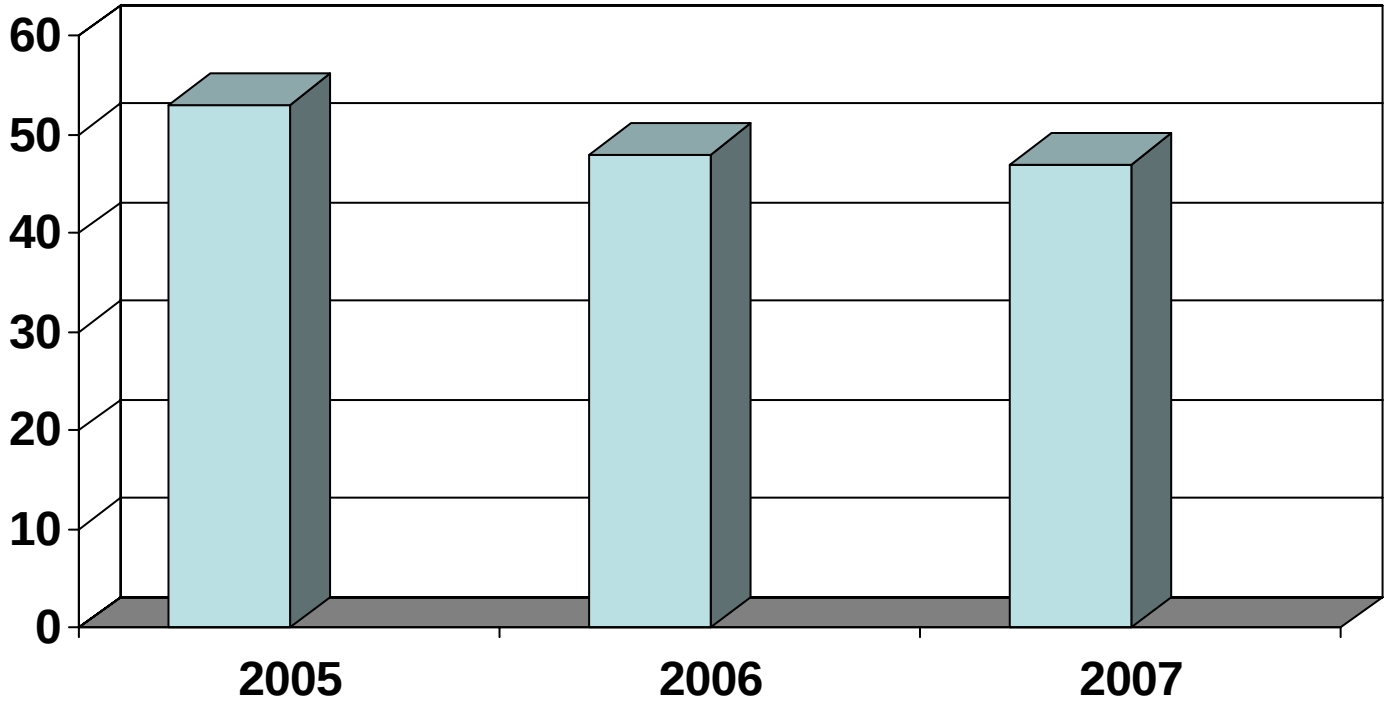
2008

www.epa.gov/comptox

CTRP Budget History



Peer Reviewed Publications by NCCT Staff



~3.8/Senior Investigator/year

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What is Center?

Source: Merriam-Webster dictionary
Main entry: Center
Pronunciation: ‘sen-tar
Function: Noun
Etymology: Middle English *centre,* from Middle French, from Latin *centrum,* from Greek *kentrum,* sharp point, center of a circle, from *kentein* to prick, probably akin to Old high German *hantag,* pointed
Date: 14th Century

1a: the point around which a circle or spear is described….
2a: a point, person, or thing that is most important or pivotal in relation to an indicated activity, interest or condition; b: a source from which something originates; c: a group of nerve cells have a common function; d: a region of concentrated population; **e: a faculty providing a place for a particular activity or service**

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Main Aspects of NCCT Directions (Impact, Innovation and Critical Mass)

- Service
  - Participation in research originating largely outside of the NCCT
    - Arsenic BBDR
  - Coordination of Communities of Practice
- Education
  - Postdoctoral Fellows
  - Specialty courses (traditional and web based)
- Research
  - Activities largely originating as result of NCCT
    - ToxCast
    - Virtual Liver
    - Virtual Embryo

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Major Comment Areas from BOSC II

- Cum Risk CoP (and others such as Cross-Species, Multi-Media Fate)
- Relationship(s) to the STAR Centers
- Strategic Plan for data collection, management and integration
- Additional training mechanisms, such as NIH K Awards
- Provide more detailed workplan on the Virtual Liver
- Recruitments, particularly those with data management skills
- Regularly scheduled plan for communication and updates
- Invite PO to BOSC reviews, engage the Regional Risk Assessors

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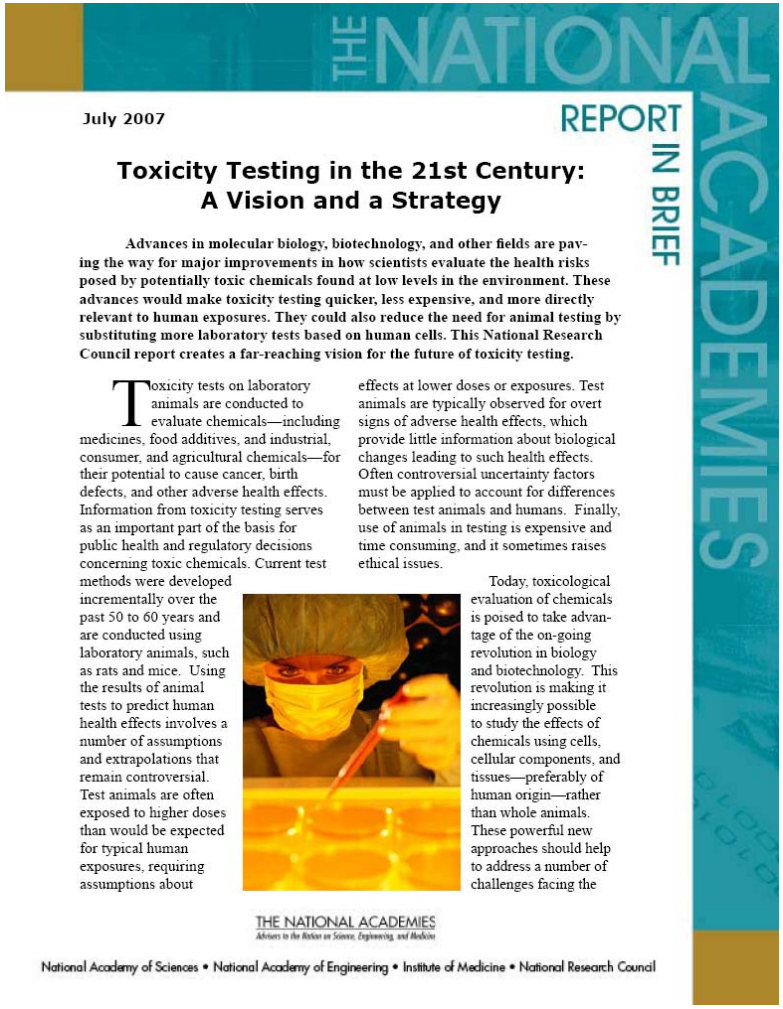
Comings and Goings

- **Arrivals**
  - **Richard Judson, Title 42 Bioinformatician**
  - **Imran Shah, Title 42 Systems Biologist**
  - **Thomas Knudsen, Title 42 Systems Biologist**
  - **Postdoctoral Fellows**
    - **David Reif, Vanderbilt Dept of Human Genetics**
    - **John Wambaugh, Duke University Physics Department**
    - **Rocky Goldsmith, Duke University Dept of Chemistry**
    - **Fathi Elloumi, University of Tunisia (via NIH)**
    - **Jason Pirone (……..) (Jan 2008)**
    - **Anne Marie Petrozelli, Duke University (Jan 2008)**
  - **Lockheed Martin**
    - **Amar Singh (Scientific Systems Analyst)**

- **Departures**
  - **Melissa Pasquinelli (post doc), to NCSU School of Textiles**
  - **Michael Breen (post doc), to NERL**
  - **Amber Goetz (graduate student), to Syngenta**

NCCT Draws Support from Recent NAS Report



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REPORT IN BRIEF

July 2007

Toxicity Testing in the 21st Century: A Vision and a Strategy

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These advances would make toxicity testing quicker, less expensive, and more directly relevant to human exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells. This National Research Council report creates a far-reaching vision for the future of toxicity testing.

Toxicity tests on laboratory animals are conducted to evaluate chemicals—including medicines, food additives, and industrial, consumer, and agricultural chemicals—for their potential to cause cancer, birth defects, and other adverse health effects. Information from toxicity testing serves as an important part of the basis for public health and regulatory decisions concerning toxic chemicals. Current test methods were developed incrementally over the past 50 to 60 years and are conducted using laboratory animals, such as rats and mice. Using the results of animal tests to predict human health effects involves a number of assumptions and extrapolations that remain controversial. Test animals are often exposed to higher doses than would be expected for typical human exposures, requiring assumptions about effects at lower doses or exposures. Test animals are typically observed for overt signs of adverse health effects, which provide little information about biological changes leading to such health effects. Often controversial uncertainty factors must be applied to account for differences between test animals and humans. Finally, use of animals in testing is expensive and time consuming, and it sometimes raises ethical issues.

Today, toxicological evaluation of chemicals is poised to take advantage of the on-going revolution in biology and biotechnology. This revolution is making it increasingly possible to study the effects of chemicals using cells, cellular components, and tissues—preferably of human origin—rather than whole animals. These powerful new approaches should help to address a number of challenges facing the

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National Academy of Sciences • National Academy of Engineering • Institute of Medicine • National Research Council

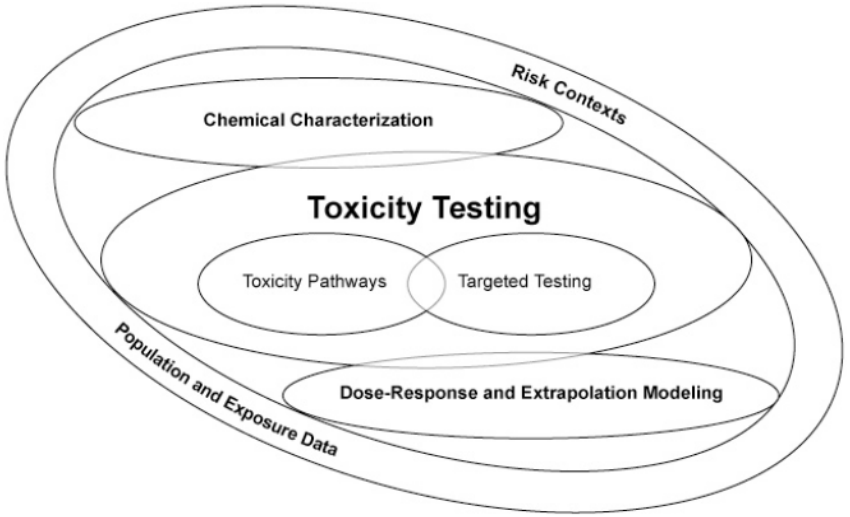

Figure 1. The committee's vision for toxicity testing is a process that can include chemical characterization, toxicity testing, and dose-response and extrapolation modeling as part of broader agency decision-making.

Kavlock et al, *ToxSci,* in press

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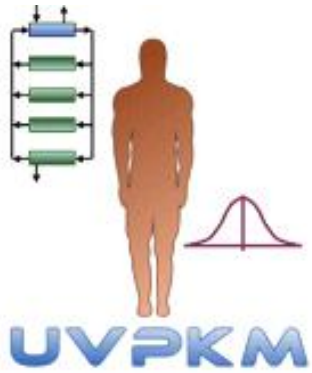

International Workshop on Uncertainty and Variability in Physiologically Based Pharmacokinetic (PBPK) Models

October 31 - November 2, 2006 Research Triangle Park, NC

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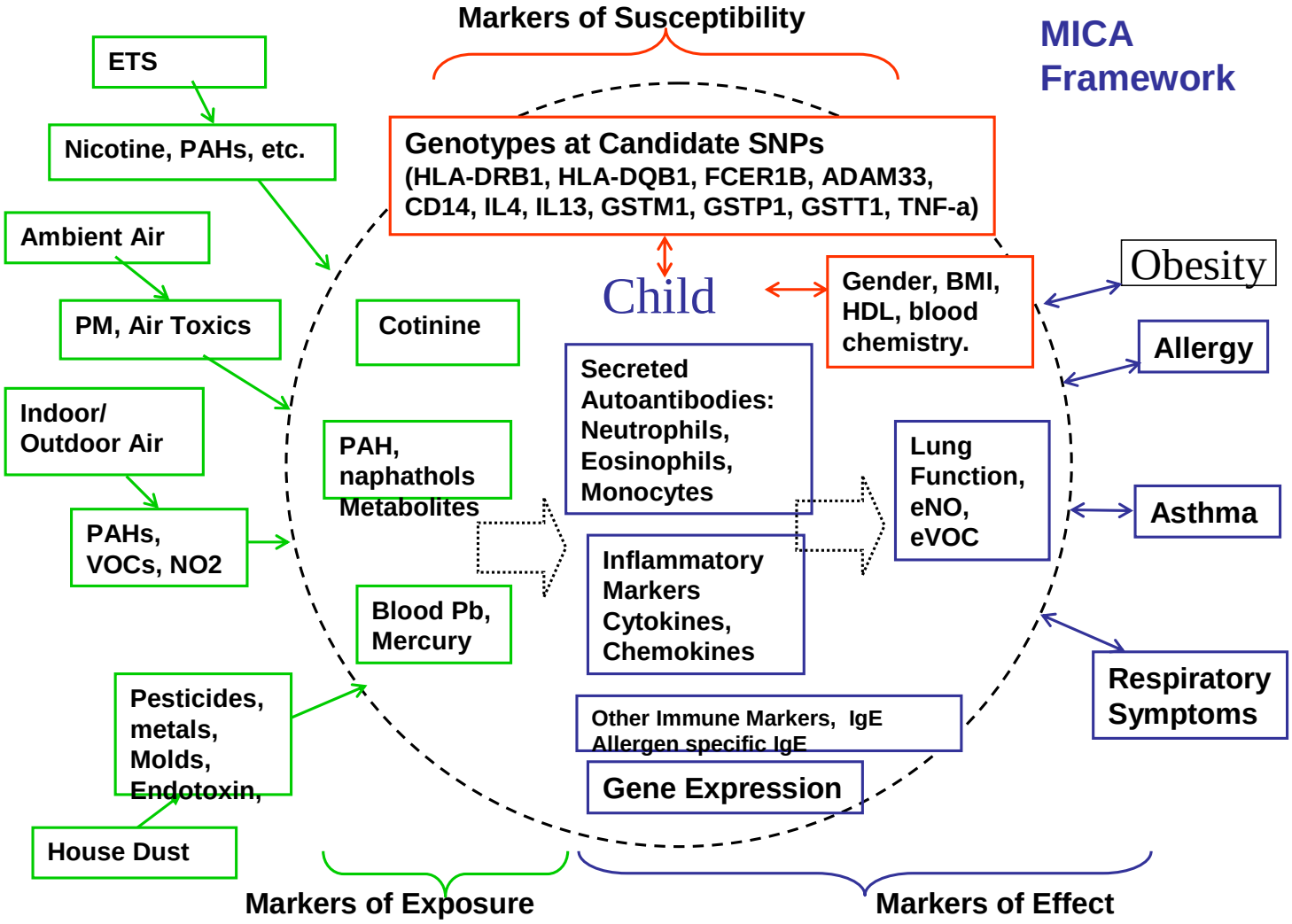

Elaine Cohen Hubal

United States Environmental Protection Agency

Other Activities within the NCCT

- **Cumulative risk of pesticides (OPs, carbamates, pyrethroids)**
- **Molecular docking of perflourinates and pyrethroids**
- **Steroidogenesis Model for the “Small Fish Project”**
- **AEP and IM/IT activities in ORD**

Next Steps

- **Full review of the program, with focus on outcomes at our 4th anniversary (February 2009)**